

ABSTRACT

Methods are presented for enhancing the natural mutation rate of micro-organisms, particularly bacteria via a modified phosphate. The novel metabolite inhibits DNA repair mechanisms in vivo resulting in a 100-200 hundred fold increase in the mutation rate of bacteria. The method yields viable cells and allows for the continuous selection of incremental traits.

The modified phosphate can also be used to randomly mutate specific genes. In particular, high rates of random mutagenesis can be readily achieved in vivo using recombinant DNA phage. The phage are amplified in mutator media containing the modified phosphate. The resultant phage can be further mutated by another round of infection and growth in mutator media. After two such rounds of amplification significant mutation rates are achieved such that each phage insert bears a novel mutation. The mutator media can also be used to mutagenize recombinant DNA plasmids in virtually any bacterial host.